

September
22th & 23th



7th EUROPEAN
CONFERENCE
ON INFECTIONS IN
LEUKAEMIA

HHV-6 update
FINAL SLIDE SET
Sept. 23rd, 2017

Mercure Sophia Antipolis Sophia Antipolis ♡ France

ECIL 7 CMV and HHV-6 update group Members

Per Ljungman (Sweden)

Rafael de la Camara (Spain)

Roberto Crocchiolo (Italy)

Hermann Einsele (Germany)

Petr Hubacek (Czech Republic)

Josh Hill (USA)

David Navarro (Spain)

Christine Robin (France)

Kate N Ward (UK)



Road map - HHV-6

- Working group
 - Kate Ward (KNW): CIHHV-6 & HHV-6 encephalitis
 - Peter Hubacek (PH): Definitions, diagnosis of infection
 - Josh Hill (JAH): HHV-6B myelosuppression, HHV-6B pneumonitis & other possible end organ disease, HHV-6 B & acute GVHD, increased all cause mortality, antiviral drugs & immunotherapy
- Suggestions further research
 - KNW, PH, JAH joint review of draft paper & slides



Introduction

HHV-6A

? Disease

HHV-6B

1⁰ infection in 1st two years of life

Exanthem subitum

Reactivation post HSCT

Encephalitis

Zerr et al., 2012; Dulery et al, 2012

Wang, 1999; Zerr, 2006

No disease has been proven with HHV-6 in patients with haematological malignancies who have not undergone HSCT

Chromosomally integrated HHV-6 (CIHHV-6)

Morisette, 2010; Pellett, 2012; Clark, 2016

HHV-6A or B always subtelomeric, prevalence about 1%

Vertical transmission

Inherited from mother or father

1 HHV-6 DNA copy*/leucocyte, & every other nucleated cell type

HHV-6 DNA also detected in hair follicles & nails (any positive suggestive of CIHHV-6)

Characteristic persistent high HHV-6 DNA level

Equivalent to leucocyte count in whole blood ($>5.5 \log_{10}$ copies/ml)

100-fold lower in serum

Variable in plasma samples

* Very rarely 2-4 copies



CIHHV-6 & disease associations

Associated with angina pectoris in a large general population screen
Gravel, 2015

One proven case of reactivation in vivo:

CIHHV-6A in child with SCID & haemophagocytic syndrome (HPS) pre-HSCT & HPS flare plus thrombotic microangiopathy post-HSCT
Endo, 2014

One possible case of reactivation in vivo:

CIHHV-6A in a patient with encephalitis post allogeneic HSCT
Hill, 2015

CIHHV-6 in donor or recipient associated with acute GVHD & CMV reactivation

Hill 2017



Findings post-HSCT according to route of HHV-6 acquisition*

Clinical/laboratory observations after allogeneic HSCT	Route of HHV-6 acquisition			
	Donor & recipient postnatal	Donor CIHHV-6 /Recipient postnatal	Donor postnatal /Recipient CIHHV-6	Donor & recipient CIHHV-6
One HHV-6 copy/ leucocyte	No	Yes	No	Yes
One HHV-6 copy/ non-haematopoietic cell	No	No	Yes	Yes
HHV-6 species/ prevalence	B/>97%	A or B/ about 1%	A or B/ about 1%	A or B About 1%
Persistent HHV-6 DNA in blood	No	Yes	+/-	Yes
Proven HHV-6 disease	Yes, encephalitis	None due to CIHHV-6	None due to CIHHV-6	None due to CIHHV-6
Response of HHV-6 DNA level to antivirals	Yes, decrease	No decrease	No decrease	No decrease

*Adapted from Ward & Clark, 2009



Definitions

- *CIHHV-6* : The viral genome has been inherited vertically and is integrated into a chromosome. HHV-6 DNA can be detected in latent form in every nucleated cell in the body.
- *HHV-6 infection (replication)*: Virus isolation by culture or detection of viral proteins or nucleic acid in any body fluid or tissue specimen. Specify source & diagnostic method. This applies to primary infection and reactivation.
- *Primary HHV-6 infection*: Detection of HHV-6 infection in an individual with no evidence of previous HHV-6 exposure. Normally this would be accompanied by HHV-6 seroconversion but HSCT recipients may not develop antibodies. Donor-derived CIHHV-6 must be excluded.



Definitions (2)

- *HHV-6 reactivation*: New detection of HHV-6 DNA in blood in an individual with evidence of previous HHV-6 exposure. Preceding primary HHV-6B infection can be assumed in individuals > 2 years old. Donor- and/or recipient-derived CIHHV-6 must be excluded.
- *CIHHV-6 reactivation*: Reactivation of the integrated virus (HHV-6A or HHV-6B) must be confirmed by virus culture plus sequencing of the viral genome to confirm identity of the viral isolate with the integrated virus.



HHV-6 Diagnostic Testing

- Quantitative PCR that distinguishes between HHV-6A & HHV-6B DNA is recommended for diagnosis of infection.
- For a given patient, repeated HHV-6 DNA testing should be performed using the same DNA extraction method, quantitative PCR, and specimen.
- If CIHHV-6 suspected, pre-HSCT whole blood or serum or cellular samples or leftover DNA from donor and/or recipient should be tested by quantitative PCR that distinguishes between HHV-6A and HHV-6B DNA. Plasma is not recommended.
- CIHHV-6 can be confirmed if there is one copy of viral DNA/cellular genome or viral DNA in hair follicles or nails, or by fluorescent in situ hybridisation (FISH).



HHV-6 Disease: Primary HHV-6 infection vs HHV-6 reactivation after allogeneic HSCT

Only 2 cases of primary HHV-6 infection have been reported. These were accompanied by fever & rash.

Lau, 1988; Muramatsu, 2009

In contrast HHV-6B reactivation is common & has been firmly associated with encephalitis.

Zerr & Ogata, 2015

HHV-6B reactivation after allogeneic HSCT: disease associations*

	Epidemiological associations	In vitro or in vivo support for causation
HHV-6B end organ disease	Encephalitis (predominantly limbic encephalitis)	Strong
	Non-encephalitic CNS dysfunction e.g. delirium, myelitis	Moderate
	Myelosuppression, allograft failure	Moderate
	Pneumonitis	Weak
	Hepatitis	Weak
HHV-6B other	Fever & rash	Strong
	Acute GVHD	Moderate
	CMV reactivation	Moderate
	Increased all-cause mortality	Weak

* Adapted from Hill & Zerr, 2016

Clinical features of HHV-6B encephalitis*

Disease onset	Usually 2-6 weeks after HSCT but can be later
Symptoms/ Signs	Confusion, encephalopathy, short term memory loss, SIADH, seizures, insomnia
Brain MRI	Often normal. Typically but not exclusively, circumscribed, non-enhancing, hyperintense lesions in the medial temporal lobes (especially hippocampus & amygdala)
CSF	HHV-6B DNA, +/-mild protein elevation, +/-mild lymphocytic pleocytosis
Prognosis	Memory defects & neuropsychological sequelae in 20-60% Death due to progressive encephalitis in up to 25% of all HSCT & up to 50% of cord blood recipients

**Adapted from Hill & Zerr,2014*



Risk factors for HHV-6B encephalitis in HSCT

- HHV-6 reactivation coincides with or precedes disease
≥ 10,000 copies/ml in blood (whole blood, serum, or plasma) correlates with HHV-6 encephalitis

Ogata, 2013; Hill, 2012

- Cord blood HSCT

Major risk factor - adjusted hazard ratio 20.00 P< .001

Hill, 2012

Incidence 8.3% cord blood & 0.5% PBMC/bone marrow HSCT

Scheurer, 2013

- Acute GVHD grades II-IV

Adjusted hazard ratio 7.5 P<.001

Hill, 2012

- Pre-engraftment syndrome

Ogata, 2015

Diagnosis of HHV-6B encephalitis

- HHV-6B encephalitis should be based on HHV-6 DNA in CSF coinciding with acute-onset altered mental status (encephalopathy), or short term memory loss or seizures.
- CIHHV-6 in donor & recipient plus other likely infectious or non-infectious causes must be excluded.
- If CIHHV-6 is detected, evidence for CIHHV-6 reactivation in the CSF or brain is necessary to implicate CIHHV-6.



Antiviral therapy for the prevention of HHV-6B encephalitis

- Two prospective, non-randomised studies of *prophylactic* foscarnet (pre or post-engraftment) did not reduce HHV-6 reactivation or encephalitis

Ogata, 2013; Ishiyama, 2012

- Two prospective, non-randomised studies of *preemptive* ganciclovir or foscarnet did not reduce HHV-6 encephalitis

Ogata, 2008; Ishiyama, 2011

Prediction & prevention of HHV-6B encephalitis

- Routine screening of HHV-6 DNA in blood after HSCT is not recommended (DIIu)
- Anti-HHV-6 prophylactic or pre-emptive therapy is not recommended for the prevention of HHV-6B reactivation or encephalitis after HSCT (DIIu)



Recent data on treatment of HHV-6B encephalitis

Retrospective study of 145 Japanese HSCT recipients with HHV-6B encephalitis

- Response rates of neurological symptoms :
 - 83.8% foscarnet monotherapy
 - 71.4% ganciclovir monotherapy
 - P=0.10
- Full dose therapy better than lower dose:
 - Foscarnet 93% vs 74% P=0.044
 - Ganciclovir 84% vs 58% P=0.047

2017



Ogata, 2017

Treatment of HHV-6B encephalitis

- Foscarnet or ganciclovir are recommended, the choice of drug being dictated by the patient's condition (Allu)
- The recommended doses are 90mg/kg b.d. for foscarnet and 5mg/kg b.d. for ganciclovir (Allu)
- Antiviral therapy should be for at least 3 weeks & until testing demonstrates clearance of HHV-6 DNA from blood and if possible CSF (BIII)
- Combined ganciclovir & foscarnet therapy can be considered (CIII)
- Immunosuppressive medications should be reduced if possible (BIII)
- There are insufficient data on the use of cidofovir to make a recommendation

Diagnosis of HHV-6B myelosuppression after HSCT

- Possible disease must be based on failed engraftment together with HHV-6 DNA in blood or bone marrow.
- CIHHV-6 in donor & recipient plus other likely infectious or non-infectious causes must be excluded.



Other possible end-organ HHV-6 diseases

- In suspected end-organ disease, other than encephalitis or failed engraftment, tissue from the affected organ should be tested for HHV-6 infection by culture, immunohistochemistry, in situ hybridization or mRNA.
- PCR for HHV-6 DNA on tissue is not recommended for documentation of HHV-6 disease since the positive predictive value is low.
- CIHHV-6 in donor & recipient plus likely pathogens & other established causes must be excluded.

Treatment for possible HHV-6 associated diseases

- No recommendation can be made.



Areas of research – HHV-6

Improved diagnostic strategies to diagnose HHV-6B end-organ disease (RNA detection to demonstrate active replication through in situ hybridization &/or reverse transcription PCR) after HSCT.

Studies of prevention & treatment strategies for HHV-6B encephalitis using novel therapeutic approaches, including new antiviral drugs & immunotherapy.

Studies of the clinical implications of CIHHV-6 in the HSCT setting & the mechanisms by which this condition affects health outcomes.

All prospective studies on HSCT patients & health outcomes, whether primarily concerned with CIHHV-6 or not, should include HHV-6A & HHV-6B testing of donor & recipient for this condition.



These slides are open for public
consultation until November 1st, 2017

Any comment, question, suggestion, should
be sent by @mail to
Kate Ward at :

k.n.ward@ucl.ac.uk

by Nov 2, 2017